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Synergistic Effects of Dopamine Agonists and Centrally Administered Neurotensin on Feeding[1]

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HAWKINS, M. F., C. A. BARKEMEYER AND R. T. TULLEY. *Synergistic effects of dopamine agonists and centrally administered neurotensin on feeding.* PHARMACOL BIOCHEM BEHAV **24**(5) 1195–1201, 1986.—Several lines of evidence indicate that neruotensin may modulate the activity of dopamine systems in the central nervous system. The present study investigated the possibility that intraperitoneal injections of the dopamine agonists l-dopa and bromocriptine would alter the aphagia produced by central administration of neurotensin. It was found that neurotensin suppressed feeding in food-deprived rats when injected into the lateral ventricle or the ventromedial hypothalamus. Food intake was not affected, however, when the peptide was placed in the lateral hypothalamus. A dose-dependent aphagia was also observed following peripheral injections of l-dopa and bromocriptine. Additionally, the anorectic effect of centrally administered neurotensin was potentiated by concurrent administration of doses of l-dopa or bromocriptine which, when given alone, had no effect on food intake. The data suggest that neurotensin aphagia may be mediated by the peptide's ability to increase the activity of dopamine systems in the central nervous system.

Bromocriptine Feeding Levodopa Neurotensin Peptides Satiety

A body of evidence has accumulated which suggests a link between the effects of neurotensin and the neurotransmitter dopamine. One area of evidence is related to the distribution of neurotensin and dopamine systems in the central nervous system. Neurotensin is heterogeneously distributed in the brain, is found in the synaptosomal fraction after ultracentrifugation, and is associated with high-affinity binding sites [22, 23, 26]. Interestingly, in many of these areas neurotensin receptor sites are found to coexist with dopamine. In the mesolimbic dopamine system axons from cell bodies in the A-10 ventral tegmental area project rostrally to terminal fields in a variety of forebrain structures including the olfactory tubercle, nucleus accumbens, and the prefrontal cortex [5]. Neurotensin and dopamine have been found to coexist in the ventral tegmentum of the mesencephalon [12,24], the nucleus accumbens [12], and the olfactory tubercle [2]. In the nigrostriatal dopamine system dopamine and neurotensin are found to coexist at the point of origin in the substantia nigra as well as in the terminal fields of the corpus striatum [2,9]. Dopamine and neurotensin are known to coexist in the tuberoinfundibular tract as well [10].

The close parallels in the distributions of neurotensin and dopamine suggest a functional relationship between the two. It has been proposed that neurotensin may act as a neuromodulator of dopamine activity in the central nervous system [21, 22, 27, 28]. The suggestion is supported by investigations of the effects of neurotensin on central dopamine activity. When injected into the cerebral ventricular system, neurotensin has been shown to increase the concentrations of dopamine and its metabolites [6, 20, 27–29]. Myers and Lee [20], for example, found with a push-pull perfusion technique that infusion of neurotensin resulted in an increase of dopamine and its metabolites from the substantia nigra of conscious, unrestrained animals. Additionally, this effect seemed to be specific for dopamine in that neurotensin infusion did not alter serotonin concentrations.

An interesting relationship between neurotensin and dopamine activity has been demonstrated in the mesolimbic system. It appears that neurotensin increases dopamine activity when it is injected into the point of origin of this system (i.e., the ventral tegmental area) and decreases dopamine activity when injected into terminal fields such as the nu-

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cleus accumbens [11, 15, 22]. Neurotensin injected into the nucleus accumbens, for example, blocks the hyperactivity produced by dopamine injected into the same locus [15]. Intra-nucleus accumbens neurotensin will also prevent the hyperactivity produced by neurotensin injected into the ventral tegmental area [14] and amphetamine-induced hyperactivity [4]. Conversely, neurotensin injected into the ventral tegmental area results in increases in general locomotor activity which are dopamine-dependent [11,13]. The behavioral data are supported by single-cell investigations which have reported that iontophoretic application of neurotensin increases the activity of dopamine neurons in the ventral tegmental area [1] and decreases the activity of dopamine cells in the nucleus accumbens [19]. These data provide compelling evidence that neurotensin modulates the activity of dopamine pathways in the central nervous system.

It is now well established that neurotensin injected into the central nervous system results in a dose-dependent reduction of food intake [7, 17, 18, 23]. This aphagia occurs following ventricular and ventromedial hypothalamic injection but not when the peptide is infused into the nucleus accumbens [7]. The experiments reported below were conducted to investigate the possibility that the anorectic property of centrally administered neurotensin would be altered by concurrent administration of dopamine agonists. For this purpose dose-response relationships were first established for neurotensin, l-dopa, and bromocriptine when these substances are administered individually (Experiment 1). Subsequently, neurotensin was injected into the cerebral ventricles and the hypothalamus in conjunction with peripheral administration of l-dopa or bromocriptine (Experiment 2).

GENERAL METHOD

Subjects

Male Sprague-Dawley rats (255–330 g) of the Holtzman strain were used. They were housed individually in suspended metal cages in a temperature-controlled (22±1°C) room with free access to food (Purina Rat Chow) and water. The lights were cycled on a 12:12 photoperiod (on 0600: off 1800). Testing was done during the light phase and was begun at 0900 each day.

A total of 111 animals were used. These were randomly assigned to one of the following treatment conditions:

1. intraperitoneal l-dopa (n=20)
2. intraperitoneal bromocriptine (n=25)
3. lateral ventricular neurotensin (n=23)
4. ventromedial hypothalamic neurotensin (n=13)
5. lateral hypothalamic neurotensin (n=6)
6. ventricular neurotensin and peritoneal bromocriptine (n=6)
7. ventromedial hypothalamic neurotensin and peritoneal bromocriptine (n=6)
8. ventricular neurotensin and peritoneal l-dopa (n=6)
9. ventromedial hypothalamic neurotensin and peritoneal l-dopa (n=6)

Surgery and Histology

Stainless steel guide cannulae were implanted in the lateral ventricle (LV), ventromedial hypothalamus (VMH), and lateral hypothalamus (LH) with the aid of a Kopf small animal stereotaxic instrument. Coordinates for the implants [25] were as follows: LV = 0.0 mm anterior to bregma, 1.6 mm lateral to the midsagittal suture, and 3.0 mm ventral to dura; VMH = 0.2 mm anterior, 0.7 mm lateral, and 8.0 mm ventral ; LH = 0.2 mm posterior to bregma, 2.0 mm lateral, and 8.0 mm ventral. The surgical techniques employed have been described elsewhere [7,8].

At the completion of testing, the animals were sacrificed with an overdose of chloroform and were perfused systemically with 0.9% saline followed by 10% phosphate-buffered Formalin. After storage in Formalin for at least 24 hours the brains were blocked at the angle of cannula entry and frozen 40 micron sections were taken through the area of implantation. The sections were mounted on microscope slides, stained with cresyl violet, and examined for the site of injection.

Injections

Neurotensin (Sigma Chemical Co.) was dissolved in sterile distilled water and was dispensed in 100 microliter aliquots into microcentrifuge tubes. The aliquots were lyophilized, placed in a desiccator, and stored frozen until the day of injection. Neurotensin was reconstituted in sterile normal saline for injection. Bromocriptine and l-dopa (Sigma Chemical Co.) were dissolved in sterile normal saline to an injection volume of 1.0 ml/kg body weight just before use. Normal saline was used for all vehicle control injections.

On the day of injection an animal was taken from its home cage, weighed, and given central and/or peripheral injections depending upon group assignment. For those animals that received intraperitoneal injections only, the injections were performed 30 minutes before the first presentation of food. When both central and peripheral injections were necessary the peritoneal injections were done 30 minutes before the central injections and food presentation. For central injections the injection volume was delivered over approximately a 90-second period and the injector was left in place for an additional 30 seconds to allow for diffusion to occur at the tip. The volume used for LV injections was 5.0 microliters; these injections were unilateral. Injections into the VMH and LH were bilateral and a volume of 0.5 microliters per side was used.

Procedure

Following postoperative recovery the animals were placed on a schedule of six-hour food availability. Food (Purina Chow) was provided from 0900 to 1500 each day. The animals were allowed to acclimate to the new schedule for 10 days. Prior to receiving food each day the animals were weighed and handled in a manner similar to the one used for injections. Body weight was recorded again at the end of the six-hour period of food access. Water was available ad lib throughout the experiment.

On day 11 baseline food intake recording was begun at intervals of 15, 30, 60, 90, 120, 180, 240, 300, and 360 minutes after food presentation. Preweighed portions of lab chow were provided and, after the specified period of time, were removed along with spillage which was collected on sheets of paper placed under the cage. The sample then was weighed again to the nearest 0.1 g and intake computed. Baseline data collection continued until food intake and body weight had stabilized (three to seven days).

Experimental testing was begun on the day following completion of the baseline phase. During the experimental phase the animals were handled as they were in the baseline

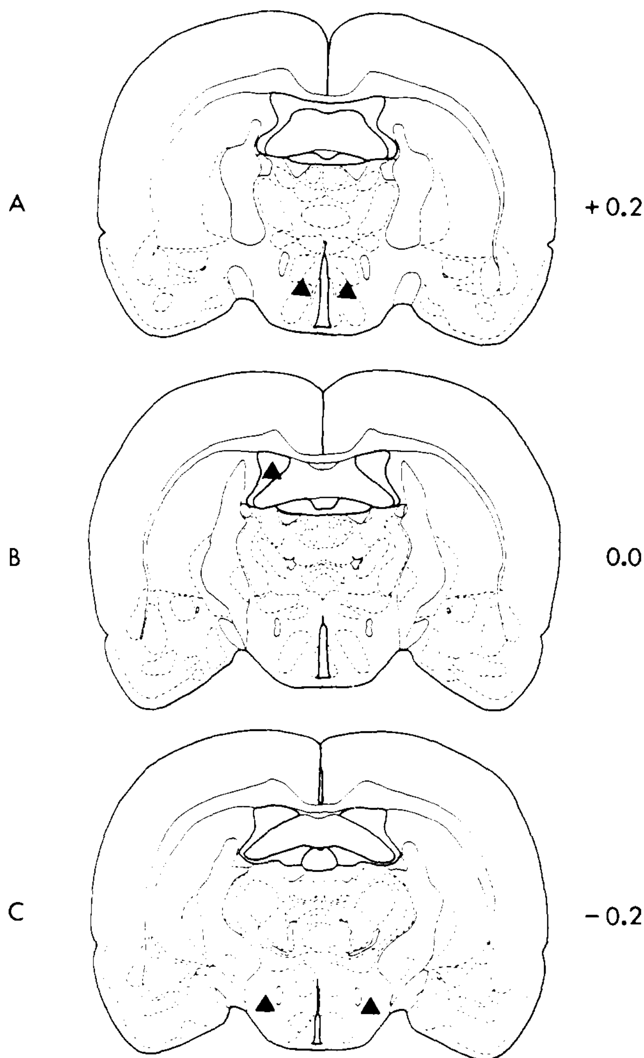

FIG. 1. Representative placement sites for implants into the ventromedial hypothalamus (A), lateral ventricle (B), and lateral hypothalamus (C). Placements are illustrated on plates from Pellegrino, Pellegrino and Cushman [25]. Numerical values represent distance from bregma in millimeters.

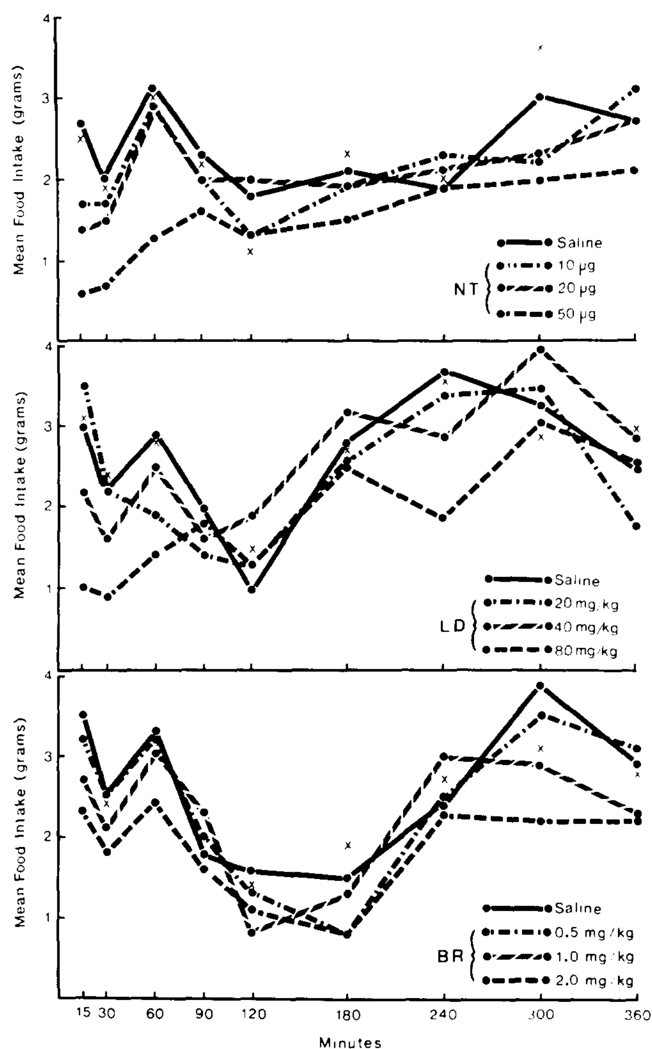

FIG. 2. Mean food intake for six hours following lateral ventricular injections of three doses of neurotensin (NT) or intraperitoneal injections of l-dopa (LD) or bromocriptine (BR) compared to saline control. Unconnected symbols (X) represent baseline food intake.

period with the exception that injections were given. All of the animals in a group received the same drug treatment on each experimental day and the sequence of the injections across days was randomly ordered. Animals were immediately returned to their home cages after injection and the first portion of food was presented. Injection days were spaced a minimum of 48 hours apart to allow for an intervening eight-hour period of food intake unaffected by drug administration.

Statistical Analysis

The data were analyzed with a repeated measures ANOVA and subsequent post-hoc tests (Duncan's Multiple Range). The alpha value for post-hoc analysis was set at 0.05.

EXPERIMENT 1

Experiment 1 was conducted to establish dose-response relationships between food intake and various concentrations of neurotensin, l-dopa, and bromocriptine. Neurotensin was microinjected into the LV, VMH, and LH. Bromocriptine and l-dopa were given intraperitoneally. Selection of the doses employed was based upon previously published research [7] and pilot data from our laboratory.

NEUROTENSIN

Method

A total of 23 animals were implanted with unilateral LV cannulae. Doses of 10, 20, and 50 micrograms of neurotensin were used. Additionally, microinjections of 2.5 micrograms/side were performed in 13 animals with bilateral VMH implants and 6 animals with bilateral LH implants.

Results

Histology. Figure 1 shows representative placements for

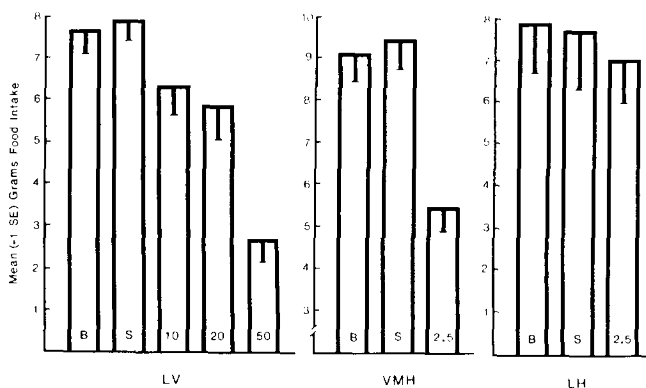

FIG. 3. Mean cumulative food intake for the first 60-minute period after injections into the lateral ventricle (LV), ventromedial hypothalamus (VMH), and lateral hypothalamus (LH). B=baseline; S=saline control; 2.5, 10, 20, and 50=micrograms of neurotensin. Verticle bars represent 1 standard error of the mean.

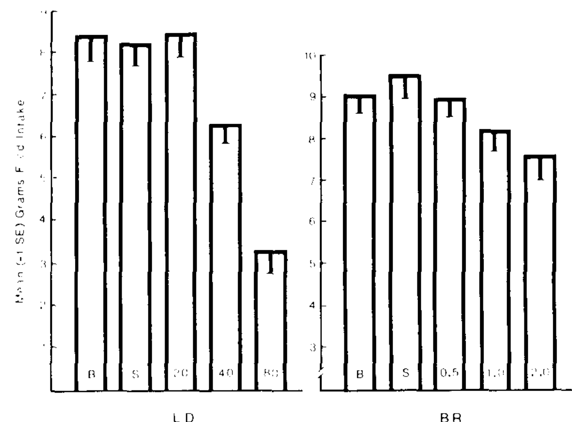

FIG. 4. Mean (−1 standard error) cumulative food intake for the first 60-minute period after intraperitoneal injection of l-dopa (LD) or bromocriptine (BR). B=baseline; S=saline control; 0.5, 1.0, 2.0, 20, 40, and 80 =mg/kg.

cannulae in the LV, VMH, and LH on plates from Pellegrino, Pellegrino and Cushman [25] with coronal plane coordinates. The data reported below and the number of subjects per group cited above are only for those animals in which histological examination confirmed accurate cannula placement.

LV injections. Six-hour food intake during the baseline, saline control, and three drug conditions is depicted in Fig. 2. As can be seen, neurotensin decreased food intake. While this effect was significant, $F(4,88)=20.99$, $p<0.0001$, and dose-dependent, the aphagic effect did not persist throughout the entire six-hour recording period. At 60 to 90 minutes after injection of neurotensin, food intake had returned to baseline and saline control levels. Therefore, the data for the first 60 minutes were analyzed to determine dose-response relationships.

Cumulative food intake for the first 60 minutes after injection is shown in Fig. 3. Saline injections did not change food intake from baseline levels while neurotensin injections produced a dose-dependent decrease in food intake, $F(4,88)=27.30$, $p<0.0001$. The 10 microgram dose depressed food intake by 20% compared to vehicle control and the 20 and 50 microgram doses decreased intake 26% and 67% respectively. Post-hoc analysis revealed that all three doses decreased food intake significantly and that the 10 and 20 microgram doses did not differ from one another.

VMH injections. The effect of neurotensin on cumulative food intake for the first 60 minutes following injection into the VMH is shown in Fig. 3. Intake was not altered by saline but decreased 43% when neurotensin was given. This effect was significant, $F(2,22)=25.64$, $p<0.0001$.

LH injections. The cumulative data for the first 60 minutes are presented in Fig. 3. As can be seen, the same dose of neurotensin which depressed food intake following injection into the VMH had no effect on eating when injected into the LH, $F(2,8)=1.73$, $p=0.24$.

L-DOPA

Method

Twenty experimentally naive animals received intraperitoneal injections of l-dopa in concentrations of 20, 40, and 80 mg/kg body weight. Injection volume was 1.0 ml/kg.

Results

Food intake for the complete six-hour period is depicted in Fig. 2. A significant main effect for drug condition was found, $F(4,76)=23.64$, $p<0.0001$. As with neurotensin injections food intake tended to return to baseline and control levels 60 to 90 minutes into the recording period. Therefore, the first 60 minutes of food intake was subjected to further analysis in order to determine dose-response relationships.

Figure 4 displays cumulative intake for the first 60 minutes. L-dopa decreased food intake significantly, $F(4,76)=33.55$, $p<0.0001$. While the 20 mg/kg dose had no effect on food intake, the 40 mg dose suppressed intake 23% compared to vehicle control and the 80 mg dose decreased intake by 60%. Post-hoc analysis revealed that the two highest doses differed significantly from one another and from the saline, baseline, and 20 mg conditions.

BROMOCRIPTINE

Method

Bromocriptine was administered intraperitoneally to 25 experimentally naive animals. The doses used were 0.5, 1.0 and 2.0 mg/kg body weight. Injection volume was 1.0 ml/kg.

Results

Six-hour food intake for the five treatment conditions is shown in Fig. 2 and cumulative intake for the first 60 minutes is presented in Fig. 4. Total six-hour intake was reduced significantly when bromocriptine was injected, $F(4,96)=32.04$, $p<0.0001$. Analysis of the data for the first 60 minutes revealed that saline injections did not change food intake from baseline levels and the effect of the 0.5 mg/kg dose was not different from the saline condition. The 1.0 mg/kg injection, however, decreased consumption 14% from the vehicle control level and the 2.0 mg/kg dose decreased intake 20%. The effects of the two higher doses differed sig-

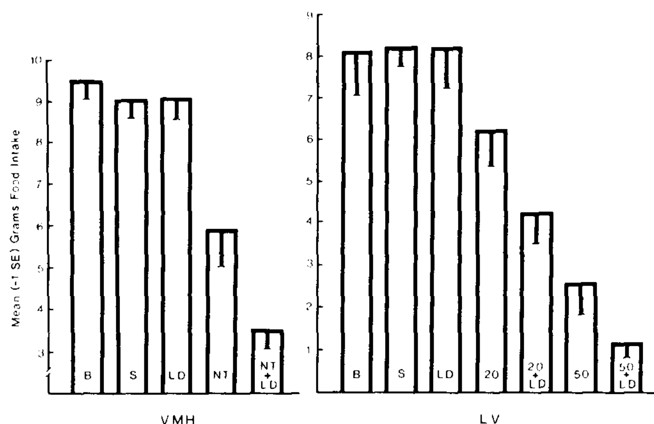

FIG. 5. Mean (−1 standard error) cumulative food intake for 60 minutes after injection of neurotensin and l-dopa in the VMH group and the LV group. B=baseline; S=saline control; LD=20 mg/kg l-dopa; NT=2.5 micrograms neurotensin/side; NT+LD=2.5 micrograms neurotensin/side + 20 mg/kg l-dopa; 20 and 50=micrograms of neurotensin.

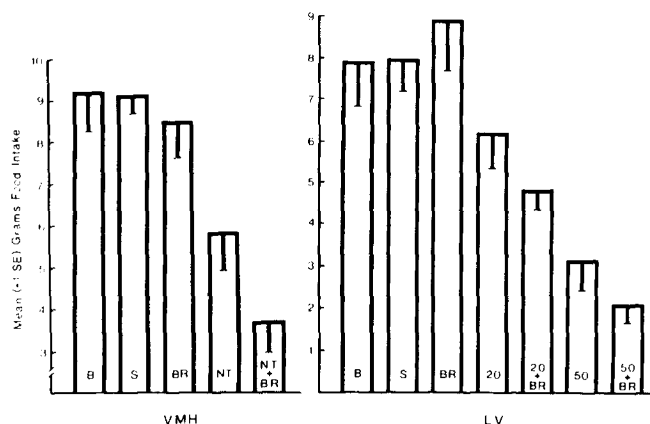

FIG. 6. Mean (−1 standard error) cumulative food intake for 60 minutes after injection of neurotensin and bromocriptine in the VMH group and the LV group. B=baseline; S=saline control; BR=0.5 mg/kg bromocriptine; NT=2.5 micrograms neurotensin/side; NT+BR=2.5 micrograms neurotensin/side + 0.5 mg/kg bromocriptine; 20 and 50=micrograms of neurotensin.

nificantly from the baseline, saline, and 0.5 mg/kg conditions but did not differ from one another.

EXPERIMENT 2

Experiment 2 was undertaken to investigate the possibility that neurotensin-induced aphagia would be affected by concurrent administration of dopamine agonists. Neurotensin was microinjected into the VMH and the LV in conjunction with intraperitoneal injections of bromocriptine and l-dopa. The doses employed were derived from the results of Experiment 1. Doses of neurotensin were selected which had been demonstrated in Experiment 1 to produce a reliable decrease in food intake. For LV injections doses of 20 and 50 micrograms were used and a dose of 2.5 micrograms/side was used for VMH injections. Doses of bromocriptine and l-dopa were selected which, when given alone, were shown in Experiment 1 to have no significant effect on food intake. Doses of 0.5 mg/kg of bromocriptine and 20 mg/kg of l-dopa were used.

NEUROTENSIN + L-DOPA

Method

Six animals implanted with bilateral VMH cannulae and 6 animals with unilateral LV implants were used. All of the subjects were experimentally naive and each was injected with saline, neurotensin alone, l-dopa alone, and neurotensin plus l-dopa. Food intake was recorded for one hour following food presentation at intervals of 15, 30, and 60 minutes.

Results

Histology. The results depicted in Fig. 1 are representative of the implants for Experiment 2.

VMH group. Cumulative intake for 60 minutes is presented in Fig. 5. As expected based upon the results of Experiment 1, a significant effect for drug condition was found, $F(4,20)=27.94$, $p<0.0001$. Post-hoc analysis revealed that food intake did not differ for the baseline, saline, and l-dopa conditions. Following neurotensin injection food intake was 35% less than the saline value; this decrease was statistically significant. Additionally, when neurotensin and l-dopa were administered simultaneously food intake dropped 62% from the saline value. This effect differed significantly from all of the others.

LV group. The results of LV injections are depicted in Fig. 5. Once again a significant drug effect was found, $F(6,30)=26.12$, $p<0.0001$. L-dopa alone had no effect on food intake. The 20 microgram dose of neurotensin alone decreased food intake significantly (25%) compared to saline. The joint action of this dose and l-dopa reduced intake by 49%, which was significantly different from all of the other treatment conditions. The 50 microgram dose of neurotensin resulted in a 70% reduction of food intake and l-dopa given simultaneously with this dose decreased intake 86%. These two effects were significantly different from the other treatments but did not differ from one another.

NEUROTENSIN + BROMOCRIPTINE

Method

Six LV and 6 VMH animals were used. The animals were experimentally naive and the procedures employed were the same as those described above for the Neurotensin + L-dopa groups.

Results

VMH group. Figure 6 shows the results of VMH injections. A significant effect on food intake was found, $F(4,20)=13.22$, $p<0.0001$. Neurotensin significantly decreased consumption from the saline value (37%) and the combination of bromocriptine and neurotensin resulted in a greater decrease in intake (61%) which was significantly different from all other values. Food intake was not affected by bromocriptine alone and the baseline and saline values did not differ.

LV group. The cumulative intake data for the LV group are presented in Fig. 6. As expected, food intake was altered significantly during the first hour, $F(6,30)=18.90$, $p<0.0001$. The baseline, saline, and bromocriptine conditions did not differ significantly. The 20 microgram dose of neurotensin

decreased food intake 23% from the saline value and the 50 microgram dose reduced intake 61%. The effects of these two doses differed significantly. When 20 micrograms of neurotensin was given in conjunction with bromocriptine, food intake was reduced by 40%; a result which was statistically equivalent to the effect of injecting 50 micrograms of neurotensin without bromocriptine. The combination of 50 micrograms or neurotensin and bromocriptine resulted in a 75% reduction in food intake. This value was significantly lower than all other values except for the 50 microgram condition.

DISCUSSION

The present data replicate our previously published finding that neurotensin suppresses food intake when injected into the lateral ventricle or the ventromedial hypothalamus [7]. Additionally, we report here for the first time that the peptide has no effect on food intake when it is infused into the lateral hypothalamus. A dose-related decrease in feeding was also observed following peripheral administration of l-dopa or bromocriptine and low doses of these dopamine agonists, which did not affect food intake when given alone, potentiated the aphagia produced by neurotensin. This suggests the possibility that neurotensin may alter feeding by increasing the activity of central nervous system dopamine systems and complements previous reports of enhanced dopaminergic activity produced by neurotensin [1, 4, 6, 11, 13–15, 19, 20, 22, 27–29].

In support of the suggestion that neurotensin aphagia is mediated by an increase in dopamine activity are the findings of Kalivas and his colleagues [11–15]. This team has found that neurotensin injected into the nucleus accumbens, a major terminal field for the mesolimbic dopamine system, produces a variety of behaviors indicative of decreased dopamine activity. Conversely, when the peptide is infused into the ventral tegmental area, the point of origin for the mesolimbic pathway, effects are produced which strongly suggest increased dopamine activity. It is interesting to note, therefore, that we have previously reported that neurotensin has no effect on feeding when it is injected into the nucleus accumbens [7]. Additionally, results of recently completed research in our laboratory have shown that microinjections of neurotensin into the ventral tegmental area result in a pronounced aphagia (manuscript in review).

The fact that both bromocriptine and l-dopa acted synergistically with neurotensin provides information regarding dopamine receptor subtypes which may be involved. Dopamine receptors are divided into two subtypes based upon pharmacological effects [3,16]. D-1 receptors are linked to adenylate cyclase within the cell and D-2 receptors are not. While l-dopa is agonistic at both D-1 and D-2 receptors, bromocriptine is agonistic at D-2 receptors only and acts as an antagonist at D-1 receptors [16]. Therefore, if it is true that neurotensin aphagia occurs as a result of the peptide's agonistic effect at dopamine synapses, our data suggest that the D-2 receptor subtype may be of primary importance.

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